Continuous negative external pressure (cNEP) reduces respiratory impairment during screening colonoscopy: a pilot study

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Background and study aims: Drugs administered during gastrointestinal procedures cause increased collapsibility of the upper airway, which may lead to respiratory impairment. We evaluated the ability of continuous negative external pressure (cNEP) to lessen respiratory impairment during screening colonoscopy.

Patients and methods: The initial 24 patients served as controls, while the next 30 received cNEP. cNEP was delivered by a soft silicone collar placed over the anterior neck. The primary endpoint was the frequency of respiratory impairment, defined as either: (i) a decline from baseline of > 4 % in oxygen saturation, or (ii) apnea lasting ≥ 20 seconds.

Results: Mean respiratory impairment episodes were 3.50 in the no-cNEP group vs. 1.92 in the cNEP group, a reduction of 45 % (P = 0.022). Apneas ≥ 20 seconds occurred in 74 % of the no-cNEP group and 28 % of the cNEP group (P = 0.002). While 42 % of the no-cNEP group required increased supplemental oxygen, this was true for only 10 % of the cNEP group (P = 0.01). cNEP adverse events were minimal.

Conclusions: During screening colonoscopy, sedation-related respiratory impairment is significantly reduced by cNEP.

ClinicalTrials.gov NCT01895062.

Introduction

Medications administered for sedation and analgesia can diminish respiratory drive and reduce tone in airway dilator muscles. This can lead to upper airway obstruction, with resultant apnea [1]. Indeed, when ventilation is assessed during endoscopic procedures, apneas are common and are associated with reduced oxygen saturation [2 – 4]. Upper airway dysfunction is of particular concern in clinical settings, such as colonoscopy, where an anesthesiologist may not be routinely present. In such circumstances, the availability of a simple to use, noninvasive device to support airway patency could be particularly beneficial.

Continuous negative external pressure (cNEP) is a new approach which modifies the spatial relationships of the soft tissue structures of the pharynx so that airway collapse is retarded. cNEP is applied by means of a soft silicone collar (Sommetrics, Inc., San Diego, California, USA) placed below the mandible which makes a seal on the anterior surface of the neck (**Fig. 1**). Tubing from the device is attached to a vacuum pump, which creates a negative pressure of 45 cm H_2O within the collar. We hypothesized that by retarding upper airway collapse, cNEP would lessen the frequency of respiratory impairment during colonoscopy.

Patients and methods

Patients

This study was conducted in adults undergoing screening colonoscopy at Scripps Green Hospital (La Jolla, California, USA). Participants were required to provide written informed consent.

Study design

All patients received standard care, as routinely provided at the study site, which includes the use of intravenous sedative and analgesic agents, the administration of oxygen at 2 L/min by nasal cannula, and monitoring according to published guidelines [5,6]. Moderate sedation was achieved by an initial bolus of 2 – 3 mg midazolam plus either 25 – 50 mg meperidine or 25 – 50 mcg fentanyl. Additional doses were administered every 2 minutes as required. If in the course of the procedure the patient's peripheral capillary oxygen saturation (SpO_2) fell below 92 %, oxygen delivery was increased.

Fig. 1 The continuous negative external pressure (cNEP) device, which makes a seal on the anterior surface of the neck so that a vacuum pump can be used to create a negative pressure within the collar.

The initial group of approximately 25 patients was to receive standard care (the "no-cNEP" group). If > 30% of this cohort had at least one episode of respiratory impairment, the next 25 – 30 patients would receive standard care with the addition of cNEP (the "cNEP" group). It was not possible to blind treatment assignment because a sham condition could not be maintained – a collar without negative pressure applied does not remain in place.
This study was approved by the Scripps Human Subjects Protection Committee (IRB-12-5897) and was registered at ClinicalTrials.gov (number NCT01895062).

Procedures

Demographic and other baseline data were collected on all enrolled patients. During the procedure, comprehensive respiratory monitoring was performed using the NOX-T3 monitor (CareFusion, San Diego, California, USA), which continuously measures oxygen saturation, as well as nasal airflow and respiratory effort.

Outcome measures

The single prespecified primary outcome measure was the frequency of respiratory impairment, defined as either: (i) a decline in SpO_2 of ≥ 4% from baseline lasting longer than 20 seconds, or (ii) an episode of apnea of at least 20 seconds [7]. Secondary outcome measures, which were considered supportive and exploratory, included the frequency and nature of apneas of at least 20 seconds' and of at least 30 seconds' duration and the frequency of falls in SpO_2 of > 4% from baseline.

Statistical analysis

Assuming the standard deviation (SD) of respiratory impairment to be 1.5, with a two-sided significance level of 0.05, a sample size of 50 total patients provided a power of 80% to detect at least a 33% decrease in mean episodes of respiratory impairment with cNEP (Student's *t* test). Such a decrease was deemed to be clinically significant.
Demographic and clinical data were summarized by calculating mean values for continuous data, and percentages for categorical data. The no-cNEP and cNEP groups were compared using the Student's *t* test for continuous data and Fisher's exact test for categorical data. All *P* values were two-sided, with an alpha of 0.05.
Propensity score matching [8] and multiple imputation modeling with sensitivity analyses [9] were performed to confirm the findings in this non-randomized study.

Table 1 Demographic details of the 54 patients who underwent screening colonoscopy either with or without the use of the continuous negative external pressure (cNEP) device.

	Overall (n = 54)	No cNEP used (n = 24)	cNEP used (n = 30)
Sex			
Female	27	9	18
Male	27	15	12
Age, years			
Mean ± SD	59.5 ± 12.5	60 ± 12.2	60 ± 13
Maximum	78	77	78
Minimum	33	34	33
BMI, kg/m^2			
Mean ± SD	26 ± 5.1	25.9 ± 4.6	26.8 ± 5.6
Maximum	49.7	35.0	49.7
Minimum	19.7	19.7	19.9
STOP-BANG score*			
Mean ± SD	2.6 ± 1.6	2.8 ± 1.5	2.4 ± 1.8
Maximum	6	5	6
Minimum	0	0	0

SD, standard deviation; BMI, body mass index.
* STOP-BANG obstructive sleep apnea score [10].

Results

Demographic and clinical characteristics

As shown in **Table 1**, all of the demographic parameters were similar between the groups, except that the cNEP patients contained a somewhat greater proportion of women. The two groups were comparable with respect to all drug doses and the duration of the procedure. The cecum was intubated in every patient.

Outcome measures

The primary outcome measure was respiratory impairment, as previously defined. The no-cNEP group experienced a mean of 3.50 episodes of respiratory impairment (95% confidence interval [CI] 2.3 – 4.64) vs. a mean of 1.92 (1.10 – 2.75) in the cNEP group ($P = 0.022$). This mean difference of 1.58 episodes represents a 45% reduction with cNEP.
Table 2 summarizes the occurrence and nature of apneas of at least 20 seconds' duration. In the no-cNEP group, 74% of patients had one or more such apnea episodes, whereas in the cNEP group, this was the case in 28% ($P = 0.002$). The mean number of apneas (all types) was 1.78 in the no-cNEP group (95%CI 0.97 – 2.60) vs. 0.38 (0.10 – 0.66) in the cNEP group. This difference was highly statistically significant ($P = 0.0006$). The mean number of obstructive apneas was reduced by more than 10-fold in the cNEP group vs. the no-cNEP group ($P = 0.006$). The findings for apneas of at least 30 seconds' duration were similar to those using the 20-second definition, but were generally even more marked in favor of cNEP.
Oxygen supplementation above the 2-L baseline level was administered in 42% (95%CI 24% – 61%) of the no-cNEP group vs. 10% (3% – 26%) of the cNEP group ($P = 0.01$). Only a single patient (cNEP group) required "jaw thrust" in response to an episode of apnea.
Using a variety of assumptions that biased against cNEP, propensity score matching and multiple imputation analyses showed

	No cNEP used (n = 23)	cNEP used (n = 29)	*P* value
Apnea, all types			
Mean number of episodes (95 %CI)	1.78 (0.97 – 2.60)	0.38 (0.10 – 0.66)	0.0006
Patients with one or more episodes (95 %CI)	74 % (53 % – 88 %)	28 % (15 % – 46 %)	0.0018
Obstructive apnea			
Mean number of episodes (95 %CI)	0.91 (0.31 – 1.61)	0.07 (0 – 0.22)	0.0061
Patients with one or more episodes (95 %CI)	39 % (22 % – 59 %)	7 % (1 % – 23 %)	0.0066
Central apnea			
Mean number of episodes (95 %CI)	0.74 (0.11 – 1.22)	0.31 (0.06 – 0.56)	NS
Patients with one or more episodes (95 %CI)	39 % (22 % – 59 %)	24 % (12 % – 42 %)	NS
Mixed apnea			
Mean number of episodes (95 %CI)	0.13 (0.03 – 0.38)	0.0 (0 – 0)	0.046
Patients with one or more episodes (95 %CI)	13 % (3 % – 38 %)	0 % (0 % – 0 %)	NS

CI, confidence interval; NS, not significant.

Table 2 Comparison in the 52 evaluable patients of the occurrence and nature of apneas of at least 20 seconds' duration between the groups managed with and without the use of the continuous negative external pressure (cNEP) device.

that the cNEP effect remained robust in spite of the sex imbalance and other possible confounders (data not shown).

Adverse events

In 12 of the 30 patients who used the cNEP device (40 %), mild cutaneous erythema was noted at the site of contact of the cNEP collar with the neck. In all cases this resolved within 20 minutes without sequelae. No other adverse events were observed, and there were no clinically significant differences in vital signs between the two groups at any point.

Discussion

This is the first report demonstrating the benefit of cNEP in reducing sedation-related respiratory impairment. cNEP not only significantly reduced the frequency of respiratory impairment, it also significantly reduced the number of apneas of all types and, even more markedly, obstructive apneas. Moreover, cNEP was associated with reduced need to increase supplemental oxygen. These broad and consistent effects indicate that cNEP may be an effective method for preventing respiratory compromise due to airway obstruction associated with the use of sedatives and opiate analgesics for endoscopic procedures.

In accordance with its postulated mechanism of action, cNEP strikingly reduced the occurrence of obstructive apneas but not of central apneas, which are the result of sedative medications on respiratory drive. There was only a single intervention to relieve airway obstruction in the entire cohort, even though 17 patients in the no-cNEP group and five in the cNEP group had at least one apnea episode of at least 30 seconds' duration. Indeed, seven of the episodes (six in the no-cNEP group) were longer than 1 minute in duration. This suggests that the clinical staff may not have detected even sustained apnea in many patients. This is consistent with a previous study showing that sedation-related apneas are not well appreciated by clinical assessment [2].

This study has several limitations. The protocol called for consecutive enrollment to the no-cNEP group, then to the cNEP group, in order to verify that respiratory impairment occurred frequently enough in controls to justify exposing patients to cNEP. We believe that these non-randomized results are nonetheless robust because demographics (except sex) and all procedure characteristics were quite similar between the groups. Propensity score and sensitivity analyses showed the results to be sustained even after adjustment for sex imbalance, as well as for other possible confounders.

Because it was impossible to maintain a sham cNEP condition, treatment assignment could not be masked. However, evaluation bias is unlikely as the key outcome measures, including the components of the primary endpoint, were recorded and analyzed electronically, avoiding observer bias [11, 12].

These findings have several implications for gastroenterologists. Colonoscopy is one of the most common gastroenterology procedures performed with moderate sedation. Our observations, using sensitive respiratory monitoring equipment, build upon previous studies [2, 3] which indicate that apnea is common in this setting and may not be well recognized by endoscopy personnel. The frequency and duration of apneas, some of which were associated with declining oxygen saturation, indicate the potential to adversely affect patient safety. Notably, respiratory impairment is the most common specific cause of medical liability cases associated with monitored anesthesia care [13].

In conclusion, in this pilot study cNEP dramatically reduced the occurrence of respiratory impairment, especially obstructive apneas, and the need for increased supplemental oxygen delivery. Because it is simple to use and appears to be well tolerated, if these results are confirmed, cNEP could prove to be a valuable adjunct to improving the safety of procedures involving endoscopy with mild-to-moderate sedation.

Competing interests: Dr Klein is a consultant to and shareholder of Sommetrics, Inc. Dr Rose is an employee of and shareholder of Sommetrics, Inc. The other authors have no conflicts of interest.

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References

1 *Hillman DR*, *Platt PR*, *Eastwood PR*. The upper airway during anesthesia. Br J Anaesth 2003; 91: 31 – 39
2 *Vargo JJ*, *Zuccaro GJr*, *Dumot JA* et al. Automated graphic assessment of respiratory activity is superior to pulse oximetry and visual assessment for the detection of early respiratory depression during therapeutic upper endoscopy. Gastrointest Endosc 2002; 55: 826 – 831
3 *Cacho G*, *Perez-Calle JL*, *Barbado A* et al. Capnography is superior to pulse oximetry for the detection of respiratory depression during colonoscopy. Rev Esp Enferm Dig 2010; 102: 86 – 89
4 *Beitz A*, *Riphaus A*, *Meining A* et al. Capnographic monitoring reduces the incidence of arterial oxygen desaturation and hypoxemia during propofol sedation for colonoscopy: A randomized, controlled study (ColoCap study). Am J Gastroenterol 2012; 107: 1205 – 1212
5 American Society for Gastrointestinal Endoscopy Standards of Practice Committee. Sedation and anesthesia in the GI endoscopy suite. Gastrointest Endosc 2008; 68: 815 – 826
6 American Society for Gastrointestinal Endoscopy. Guidelines for safety in the gastrointestinal endoscopy unit. Gastrointest Endosc 2014; 79: 363 – 372
7 *Iber C*, *Ancoli-Israel S*, *Chesson A* et al. The AASM manual for scoring of sleep and associated events: rules, terminology and technical specifications. 1st: edn. Westchester, Illinois, USA: American Academy of Sleep Medicine; 2007
8 *Austin PC*. An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivariate Behav Res 2011; 46: 399 – 424
9 *Donders AR*, *van der Heijden GJ*, *Stijnen T* et al. Review: a gentle introduction to imputation of missing values. J Clin Epidemiol 2006; 59: 1087 – 1091
10 *Chung F*, *Yegneswaran B*, *Liao P* et al. STOP questionnaire: a tool to screen patients for obstructive sleep apnea. Anesthesiology 2008; 108: 812 – 821
11 *Lesser DJ*, *Haddad GG*, *Bush RA* et al. The utility of a portable recording device for screening of obstructive sleep apnea in obese adolescents. J Clin Sleep Med 2012; 8: 271 – 277
12 *Cairns A*, *Wickwire E*, *Schaefer E* et al. A pilot study for the NOX T3TM portable monitor for the detection of OSA. Sleep Breath 2014; 18: 609 – 614
13 *Bhananker SM*, *Posner KL*, *Cheney FW* et al. Injury and liability associated with monitored anesthesia care: a closed claim analysis. Anesthesiology 2006; 104: 228 – 234